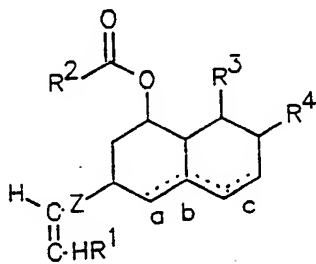


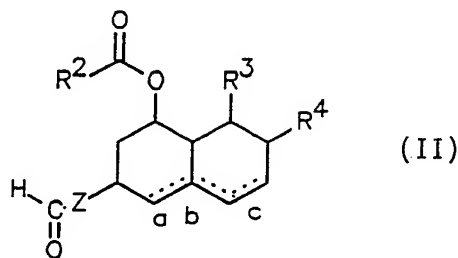


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB92/00920 <b>(22) International Filing Date:</b> 21 May 1992 (21.05.92)  <b>(30) Priority data:</b> 9111192.2                      23 May 1991 (23.05.91)                      GB  <b>(71) Applicant (for all designated States except US):</b> BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> TODD, Richard, Simon [GB/GB]; 33 Gore Road, Burnham, Buckinghamshire SL1 8AB (GB). REEVE, Maxwell [GB/GB]; 110 Southfield Park, Bartlemas Close, Oxford OX4 2BA (GB).		<b>(74) Agents:</b> SHEARD, Andrew, Gregory et al.; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>

**(54) Title:** SYNTHETIC PROCESS

(I)



(II)

**(57) Abstract**

Compounds of general formula (I), wherein  $R^1$  represents a  $C_{1-8}$  alkyl group;  $R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $C_{3-8}$  cycloalkyl ( $C_{1-8}$ )alkyl,  $C_{1-8}$  hydroxyalkyl,  $C_{1-8}$  alkylthio, phenyl, substituted phenyl or  $C_{1-6}$  alkyl substituted with an optionally substituted phenyl group.  $R^3$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $CO_2(C_{1-8})$ alkyl,  $CO_2(C_{2-8})$ alkenyl,  $C_{1-8}$  alkylthio, ( $C_{1-2}$ )alkyl  $CO_2(C_{1-8})$ alkyl or  $C_{1-8}$  aldehydoalkyl where the aldehyde function is protected by a suitable protecting group (for example, an acetal such as a dimethyl acetal);  $R^4$  represents a hydrogen atom,  $C_{1-8}$  alkyl or  $C_{2-8}$  alkenyl;  $Z$  represents a group  $(CH_2)_n$  or a branched alkyl chain;  $n$  is 0 to 8; and each of  $a$ ,  $b$  and  $c$  is independently a single or double bond; can be prepared relatively easily and in good yield at room temperature by reacting a compound of general formula (II), wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula (I); with a compound of general formula (III):  $CHI_2R^1$  wherein  $R^1$  is as defined in general formula (I); in the presence of metal ions such as chromium (II) ions. The severe conditions of the Wittig reaction can therefore be avoided. Compounds of formula (I) are useful intermediates in the synthesis of mevinic acids, which are potent inhibitors of HMG-CoA reductase and which are useful in the treatment of hypocholesterolaemia and hyperlipidaemia.

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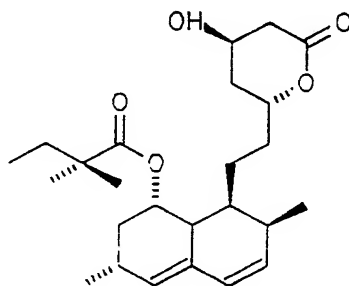
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SYNTHETIC PROCESS

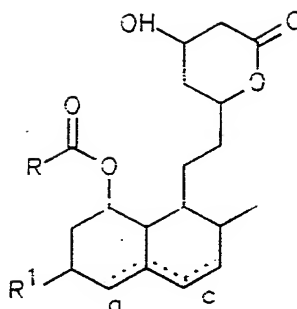
This invention relates primarily to novel synthetic procedures and compounds which are useful in the synthesis of a range of mevinic acids.

A number of mevinic acids which can formally be regarded as decalin derivatives, have been reported to be potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase), the rate limiting enzyme in the biosynthesis of cholesterol in mammals including man, and as such are useful in the treatment of hypercholesterolaemia and hyperlipidaemia.

Thus W F Hoffman et al (J. Med. Chem., 29, 849-852 (1986)) have reported the synthesis and testing of a compound now known as simvastatin, having the structure



EP-A-0251625 (Inamine) discloses compounds of structure



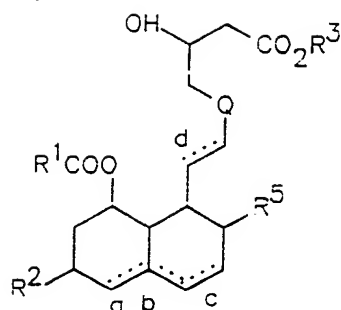
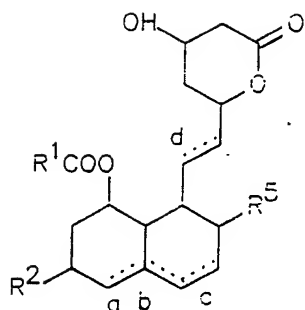
where R is similar to the corresponding group in the compounds described above,  $R^1$  is a group of formula  $CH_2OH$ ,  $CH_2OCOR^3$ ,  $CO_2R^4$  or  $CONR^6R^7$  wherein  $R^3$ ,  $R^4$ ,  $R^6$  and  $R^7$  can cover a range of alkyl, alkoxy or aryl groups, and the dotted lines represent single or double bonds.

The compounds disclosed have been generally obtained by fermentation of a suitable microorganism, or have been chemically derived from compounds obtained from such fermentations. However, a procedure based totally on chemical synthesis would have significant advantages over a fermentation procedure on grounds of flexibility, yield, ease of purification and hence cost.

WO-A-9100280 discloses the total synthesis of a group of HMG-CoA reductase inhibiting mevinic acids.

Specifically, this publication describes the synthesis of compounds of the general formula:

5



10      wherein:

R<sup>1</sup> represents a C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyl(C<sub>1-8</sub>)alkyl, C<sub>2-8</sub> alkenyl, or C<sub>1-6</sub> alkyl substituted with an optionally substituted phenyl group;

15

R<sup>2</sup> represents a C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, group or a C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, or C<sub>2-5</sub> alkynyl group substituted with a substituted phenyl group;

20

R<sup>3</sup> represents a hydrogen atom or a substituent R<sup>4</sup> or M;

R<sup>4</sup> represents a C<sub>1-5</sub> alkyl group, or a C<sub>1-5</sub> alkyl group substituted with a group chosen from substituted phenyl, dimethylamino and acetyl amino;

25

R<sup>5</sup> represents a hydrogen atom or a methyl or ethyl group, except that when R<sup>2</sup> is methyl then R<sup>5</sup> is not methyl;

30

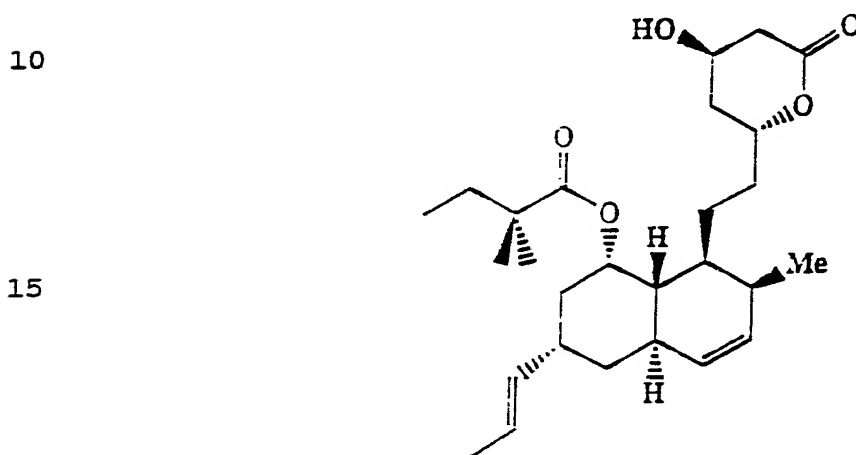
M represents a cation capable of forming a pharmaceutically acceptable salt;

Q represents C=O or CHOH; and

each of a, b, c, and d is independently a single or

double bond except that when a and c are double bonds then b is a single bond.

In particular the document describes the synthesis of  
5 (1S,2S,4aR,6S,8S,8aS,4'R,6'R)-6'-{2-(1,2,4a,5,6,7,8, 8a-octahydro-2-methyl-8-[(2'',2''-dimethyl-1''-oxobutyl)-oxy]-6- [(E)-prop-1-enyl]-1-naphthalenyl)ethyl}- tetrahydro-4'- hydroxy-2H-pyran-2'-one which has the structure:



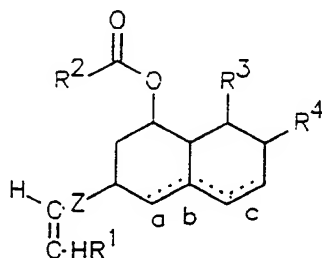
20 Pioneering as the work disclosed in WO-A-9100280 is, however, there is still room for further improvement in the synthetic methodology used, not least to enable the synthesis to be readily scaled up from the laboratory to pilot plant or production scale.

25 One of the steps used in the synthesis is the conversion of an aldehyde substituent on the decalin ring to an alkenyl substituent. In WO-A-9100280, this conversion is carried out either by a route involving sulphone derivatives and mercury amalgam, which because of its  
30 high toxicity is obviously unsuitable for use on a large scale, or by the Wittig reaction. Although the Wittig reaction proceeds satisfactorily, the reaction temperature must be kept at about -78°C to avoid

decomposition of the ylid starting material.

It has now been found that other conditions and reactants may be used to enable the reaction to proceed at or near room temperature.

According to a first aspect of the invention there is provided a process for the preparation of a compound of general formula I



I

wherein

$R^1$  represents a  $C_{1-8}$  alkyl group;

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{1-8}$  hydroxyalkyl,  $C_{1-8}$  alkylthio, phenyl, substituted phenyl or  $C_{1-6}$  alkyl substituted with an optionally substituted phenyl group.

$R^3$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $CO_2(C_{1-8})$ alkyl,  $CO_2(C_{2-8})$ alkenyl,  $C_{1-8}$  alkylthio,  $(C_{1-2})$  alkyl  $CO_2(C_{1-8})$ alkyl or  $C_{1-8}$  aldehydoalkyl where the aldehyde function is protected by a suitable protecting group (for example, an acetal such as a dimethyl acetal);

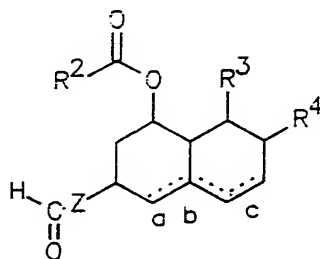
$R^4$  represents a hydrogen atom,  $C_{1-8}$  alkyl or  $C_{2-8}$  alkenyl;

Z represents a group  $(CH_2)_n$  or a branched alkyl chain;

5      n is 0 to 8;

and each of a, b and c is independently a single or a double bond;

10      the process comprising reacting a compound of general formula II



20                      II

25      wherein  $R^2$ ,  $R^3$ ,  $R^4$ , Z, a, b and c are as defined in general formula I; with a compound of general formula III



30      wherein  $R^1$  is as defined in general formula I;

in the presence of metal ions such as chromium ions.

As used herein the term " $C_{1-8}$  alkyl" refers to a straight



chain or branched chain hydrocarbon group having from one to eight carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertbutyl, pentyl, neopentyl, hexyl, heptyl and octyl.

As used herein the term " $C_{2-8}$  alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to eight carbon atoms and having in addition one or more double bonds, each of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl and 2-methyl-2-propenyl.

As used herein, the term " $C_{2-8}$  alkynyl" refers to a straight or branched chain hydrocarbon group having from one to eight carbon atoms and having in addition one or more triple bonds. This term would include for example, propargyl and 1- and 2- butynyl.

As used herein the term " $C_{1-8}$  hydroxyalkyl" refers to straight chain or branched chain alkyl groups having from one to eight carbon atoms, and in addition having one or more hydroxyl groups. Illustrative of such hydroxyalkyl groups are hydroxymethyl, hydroxyethyl, and hydroxypropyl.

As used herein the term " $C_{1-8}$  alkylthio" refers to straight chain or branched chain alkyl groups having from one to eight carbon atoms, and in addition having one or more thio groups. Illustrative of such alkylthio groups are thiomethyl, thioethyl, and thiopropyl.

As used herein the term " $C_{1-8}$  aldehydoalkyl" refers to

straight chain or branched chain alkyl groups having from one to eight carbon atoms, and in addition having one or more aldehyde groups. Illustrative of such aldehydoalkyl groups are ethanal, and propional.

5

As used herein, the term " $C_{3-8}$  cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

10

The term "substituted" as applied to a phenyl or other aromatic ring, means substituted with up to four substituents each of which independently may be  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, hydroxythiol, amino, halo (including fluoro, chloro, bromo and iodo) trifluoromethyl or nitro.

15

As mentioned above, one advantage of this olefination reaction is that it can be carried out at room temperature whereas for the Wittig reaction which was used previously it was necessary to cool the reaction mixture to  $-78^{\circ}\text{C}$  which is a marked disadvantage, especially if the reaction is to be carried out on a large scale.

20

25

Although the ions of other metals can be used in the reaction, it appears that the olefination proceeds most effectively in the presence of chromium ions such as chromium (II) ions. A suitable source of chromium (II) ions is chromium (II) chloride. Alternatively chromium (II) ions can be obtained by the reduction of a chromium (III) compound, for example chromium (III) chloride using a mild reducing agent such as zinc.

30

It has been found that the reaction works particularly

well in the case where  $R^1$  is a methyl group.

5 A further advantage of the use of this olefination reaction is that the ratio of E and Z products can be controlled simply by changing the solvent in which the reaction is carried out. Suitable solvents for the reaction include tetrahydrofuran and dimethylformamide and it has been found that tetrahydrofuran is a particularly useful solvent if a large proportion of the  
10 E isomer product is required. A ratio of E:Z isomers of as high as 15:1 has been achieved when the reaction is carried out in tetrahydrofuran, whereas with the Wittig reaction, the predominant product is the Z isomer.

15 The use of 1,1-diiodoalkanes in the presence of chromium (II) ions in the olefination of simple aldehydes is known as the Takai reaction (J. Am. Chem. Soc., (1987), 109, 951-953, Takai, K. et al).

20 While Takai et al reacted aldehydic hydrocarbons with 1,1-diiodoalkanes, it has now been discovered that the Takai reaction can be applied to much more complex aldehydes, including those substituted with polar  
25 substitutes and comprising a bulky nucleus. The reaction has in fact proved to be remarkably successful, with yields of over 80% being achieved.

Compounds of general formulae I and II are new and constitute second and third aspects of the invention.  
30 Preferred compounds include those in which, independently or in any compatible combination:

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl or  $C_{1-8}$  hydroxyalkyl;

$R^3$  represents  $\text{CO}_2\text{C}_{1-8}$  alkyl;

$R^4$  represents a methyl group;

5     Z is  $(\text{CH}_2)_n$ ;

n is 0; and

a and b are single bonds and c is a double bond; and

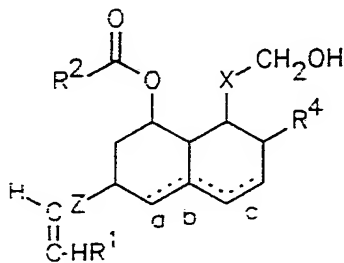
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in compounds of formula I,  $R^1$  is a methyl group.

A particularly preferred compound of formula I is ethyl  
(1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-6-  
15     [(E)-prop-1-enyl]-2-methyl-8-(2,2-dimethylbutyryloxy)  
naphthalene-1-carboxylate.

A particularly preferred compound of formula II is  
ethyl(1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-  
20     6-formyl-2-methyl-8-(2,2-dimethylbutyryloxy)naphthalene-  
1-carboxylate.

Compounds of general formula I in which  $R^3$  has an ester  
group can be reduced to give compounds of general formula  
25     IV



30

IV

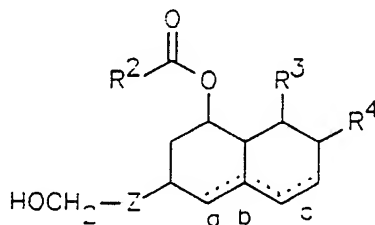
wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula I;

$X$  is  $(CH_2)_m$  or a branched alkyl chain; and  $m$  is 0 to 2

using a reducing agent such as lithium aluminium hydride or lithium borohydride or alkyl derivatives of either of them. A particularly suitable reducing agent for the reaction is lithium triethylborohydride and it is preferred that the reaction be carried out in a solvent such as tetrahydrofuran at a temperature of between  $-20^\circ C$  and room temperature. The reaction proceeds particularly satisfactorily at about  $0^\circ C$ .

Compounds of formula IV wherein  $X$  is  $(CH_2)_m$  and  $m$  is 0 are known from WO-A-9100280, however other compounds of formula IV are new and all of the compounds of formula IV are useful intermediates in the preparation of mevinic acids.

Compounds of formula II can be prepared from compounds of formula V



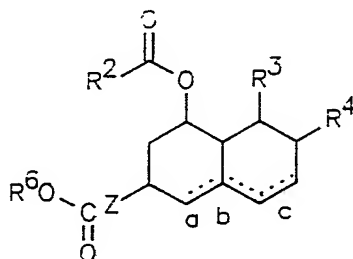
V

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general

formula I;

by oxidation with a mild oxidising agent which may be for example pyridinium dichromate in the presence of activated molecular sieves and acetic acid. The reaction can be performed in any suitable inert, aprotic solvent such as dichloromethane and will generally be carried out under an inert atmosphere such as argon.

Compounds of formula V can be prepared from compounds of formula VI



VI

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ , *a*, *b* and *c* are as defined in general formula I and

$R^6$  is a  $C_{1-8}$  alkyl straight chain alkyl group;

by selective reduction of the ester group attached to the 6-position of the decalin ring system.

In principle, selective reduction can be achieved by protecting any other groups liable to reduction, such as the ester group at the 8-position and the ester group at the 1-position in preferred embodiments of the invention.

Reduction made selective by protection in this way is largely conventional, and is the route followed in WO-A-9100280.

5 It has now been discovered that, possibly due to unusual steric factors resulting from the spatial configuration of the decalin-based ring system it is not necessary to protect ester, or even other vulnerable groups at positions other than the 6- position. Direct reaction  
10 with a reducing agent, without protection of other groups, results in selective reduction at the 6-position automatically. While steric factors are suspected to be the reason for this quite unexpected selectivity, the precise mechanism is not clear. This selective reduction  
15 of an ester group in a compound containing two or more ester groups forms a further aspect of the invention, according to which there is provided a process for the selective reduction of a compound of general formula VI as defined above, the process comprising reacting a  
20 compound of general formula VI, in which at least the ester groups at the 6 and 8-positions are unprotected, with a reducing agent.

In order to promote the selective reduction of the ester  
25 at the 6-position, rather than the ester group at the 8-position,  $R^2$  (at the 8-position) will generally be a more bulky group than  $R^6$  (at the 6-position). Suitable reducing agents for this reaction include complex hydrides such as lithium aluminium hydride, lithium  
30 borohydride or their alkyl derivatives; a particularly preferred agent is lithium triethylborohydride.

The reaction can be performed in any suitable aprotic, inert solvent with tetrahydrofuran being preferred.

Even when the  $R^3$  substituent (at the 1-position) contains an ester group, the reaction still proceeds in a high yield and with selective reduction of the ester group attached to the 6-position of the decalin ring. A particularly high degree of selectivity is obtained when  $R^3$  is an ester group in which the ester carbon is directly connected to the decalin ring and in this case, yields of over 95% of the product of general formula V have been obtained.

Compounds of general formulae V and VI are novel and comprise further aspects of the invention. Preferred compounds include those in which, independently or in any compatible combination:

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl or  $C_{1-8}$  hydroxyalkyl;

$R^3$  represents  $CO_2(C_{1-8})$ alkyl;

$R^4$  represents a methyl group;

Z is  $(CH_2)_n$ ;

n is 0; and

a and b are single bonds and c is a double bond; and

in compounds of general formula VI,  $R^6$  is methyl.

A particularly preferred compound of general formula V is:

ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8, 8a- octahydro

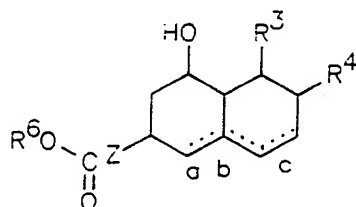


6-hydroxymethyl-2-methyl-8-(2, 2- dimethylbutyryloxy)  
naphthalene-1-carboxylate.

A particularly preferred compound of formula VI is:

ethyl (1S, 2S, 4aR, 6S, 8S, 8aS)-1,2,4a,5,6,7,8, 8a-  
octahydro-6-methoxycarbonyl-2-methyl-8-(2, 2-  
dimethylbutyryloxy) naphthalene-1-carboxylate.

Compounds of general formula VI can be prepared from  
compounds of general formula VII



VII

wherein  $R^3$ ,  $R^4$ , Z, a, b and c are as defined in general  
formula I and  $R^6$  is  $C_{1-8}$  alkyl;

by acylation with an appropriate acylating agent, which  
may be an acid halide of general formula VIIIA



wherein  $R^2$  is as defined in general formula I and X is Cl  
or Br.

The reaction may be carried out in an aprotic solvent

such as tetrahydrofuran in the presence of a suitable base, for example triethylamine.

Alternatively, the acylating agent may be an acid  
5 anhydride of general formula VIIIb in the presence of pyridine.



10 wherein  $R^2$  as is defined in general formula I.

Alternatively, and particularly in cases where compounds of general formulae VIIIA and VIIIb are unstable, a carboxylic acid of general formula VIIIC may be used as  
15 an acylating agent.



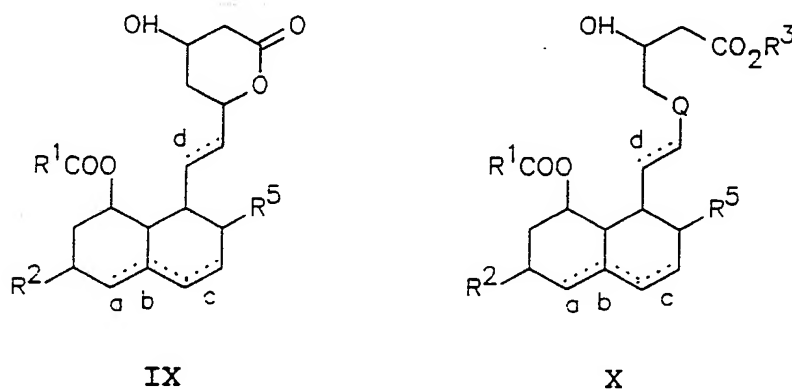
wherein  $R^2$  is as defined in general formula I. The  
20 reaction should preferably be carried out in the presence of a coupling agent such as 1,3- dicyclohexylcarbodiimide in pyridine or in an aprotic solvent such as tetrahydrofuran. Preferably, an activating agent such as dimethylaminopyridine is also present and a base such as  
25 triethylamine may also be used. A particularly suitable acylating agent for this reaction is dimethylbutyryl chloride in pyridine and the reaction temperature is ideally about 90°C.

30 Compounds of formula VII are known and can easily be prepared by a person skilled in the art.

The invention also provides a method of preparing a compound of general formula IV from a compound of general

formula VII using, sequentially, the steps described above. This method has considerable advantages over the method described in WO-A-9100280, not only because of the advantages mentioned in connection with the intermediate conversion of a compound of general formula II to a compound of general formula I, but also because the ester at the 8-position of the ring does not have to be protected in the route of this invention and therefore there are fewer steps in the synthesis thus simplifying the process and increasing the overall yield.

In still another aspect of the invention, there is provided a method for the preparation of compound of general formulae IX and X:



wherein:

$R^1$  represents a  $C_{1-8}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{2-8}$  alkenyl, or  $C_{1-6}$  alkyl substituted with an optionally substituted phenyl group;

$R^2$  represents a  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl, group

or a C<sub>1-5</sub> alkyl, C<sub>2-5</sub> alkenyl, or C<sub>2-5</sub> alkynyl group substituted with a substituted phenyl group;

R<sup>3</sup> represents a hydrogen atom or a substituent R<sup>4</sup> or M;

5 R<sup>4</sup> represents a C<sub>1-5</sub> alkyl group, or a C<sub>1-5</sub> alkyl group substituted with a group chosen from substituted phenyl, dimethylamino and acetylamino;

10 R<sup>5</sup> represents a hydrogen atom or a methyl or ethyl group, except that when R<sup>2</sup> is methyl then R<sup>5</sup> is not methyl;

M represents a cation capable of forming a pharmaceutically acceptable salt;

15 Q represents C=O or CHOH; and

each of a, b, c, and d is independently a single or double bond except that when a and c are double bonds then b is a single bond;

20 the method comprising converting a compound of general formula VII to a compound of general formula IV by the method described above, followed by converting a compound of general formula IV to a compound of general formula IX or X by an appropriate method.

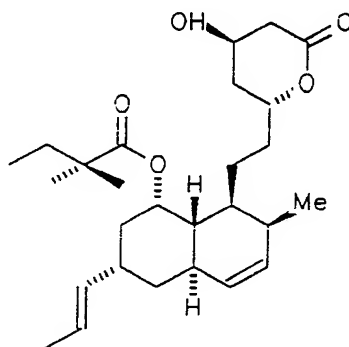
25 As mentioned above, compounds of general formulae IX and X were described in WO-A-9100280 and can be prepared from compounds of formula IV by the route described in that document.

30

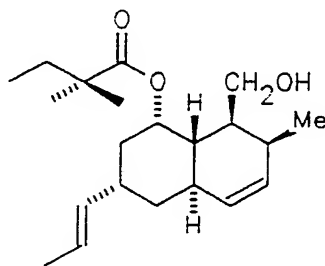
A particularly preferred compound which can be prepared by this route is:

(1S, 2S, 4aR, 6S, 8S, 8aS, 4'R, 6'R)-6'-{2- (1, 2, 4a,5,6,7,8,8a-octahydro-2-methyl-8-[(2'',2''-dimethyl-1''-oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)ethyl}-tetrahydro-4'-hydroxy-2H-pyran-2'-one

which has the formula



and which can be prepared from (1S, 3S, 4aR, 7S, 8S, 8aS)-1,2,3,4,4a,7,8, 8a-octahydro-8-hydroxymethyl -7-methyl-3-[(E)-prop-1-enyl]-1-naphthalenyl 2,2-dimethylbutyrate, a compound of general formula IV which has the structure:



The following example, which is for the purposes of illustration only, shows the synthesis of a compound of

general formula IV starting from a compound of general formula VII.

5 In each of the steps: organic solutions were dried over magnesium sulphate.

THF refers to tetrahydrofuran.

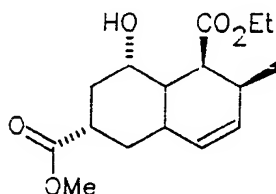
10 NMR spectra were recorded at ambient temperature in deuteriochloroform at 250 MHz for proton and 62.9 MHz for carbon unless noted otherwise. All chemical shifts are given in parts per million relative to trimethylsilane.

15 Infra red spectra were recorded at ambient temperature in solution in chloroform, or in the solid state in a potassium bromide disc.

ExampleStep 1

5 Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-8-hydroxy-6-methoxycarbonyl-2-methylnaphthalene-1-carboxylate

10



15

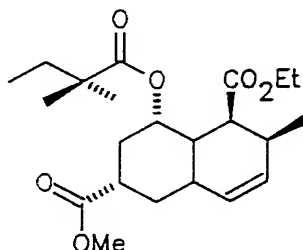
Sodium bis (trimethylsilyl)amide (1.0M in tetrahydrofuran; 144.8 mmol) was added via cannula to a stirred solution of (+) ethyl (1S,2S,4aR,6S,8S, 8aS)1, 2,4a,5,6,7,8,8a-octahydro-2-methyl-6,8naphthalene-carbolactone-1-carboxylate, (37.9g), 143.4 mmol) in dry methanol (1.6L) and cooled to between -15°C to -20°C under argon. The cold solution was stirred for 2 hours then a saturated solution of ammonium chloride (400 mL) was added in several portions. The mixture was allowed to warm to +15°C, then the methanol was evaporated under reduced pressure and the thick aqueous residue extracted with diethyl ether (1 x 500 mL, 2 x 250 mL). The combined diethyl ether extracts were washed successively with 2M aqueous hydrochloric acid (200 mL), water (200 mL), and brine (200 mL) then dried and evaporated under reduced pressure. The residue was crystallised from diethyl ether/hexane, to give three crops of the hydroxy ester product (25.8g, 61%).

delta <sub>H</sub> 5.60 (1H, ddd, J 9.8, 4.5 and 2.7 Hz), 5.40 (1H, d, J 9.8 Hz), 4.28 (1H, m), 4.15 (2H, m), 3.73 (3H, s), 3.51 (1H, d, J 6.4 Hz), 2.90 (1H, dd, J 11.6, 6.0 Hz), 2.84 (1H, m), 2.62 (1H, m), 2.38 - 2.30 (2H, m), 2.16 - 2.10 (1H, m), 1.82 (1H, ddd, 15.1, 6.1, 3.5 Hz), 1.55 - 1.35 (2H, m), 1.28 (3H, t, J 7.1 Hz), 0.91 (3H, d, J 7.2 Hz)

10      Step 2

Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-6-methoxycarbonyl-2-methyl-8-(2, 2- dimethylbutyryloxy) naphthalene-1-carboxylate.

15



A solution of the alcohol from step 1 (37.5g, 127mmol), 2,2-dimethylbutyryl chloride (68.2, 453 mmol) and 4-dimethylamino pyridine (2.1g, 17 mmol) in pyridine (1000 mL) was stirred at 90°C (oil-bath temperature) for 16 hours. The dark reaction mixture was concentrated to 100 mL and then partitioned between dichloromethane (2 x 500 mL) and 2M aqueous hydrochloric acid (500 mL). The combined organic layers were washed with water (2 x 400 mL) and saturated aqueous sodium bicarbonate solution (500 mL), then dried and evaporated under reduced pressure. The residual brown oil (52.3g) was purified by



chromatography on silica eluting with hexane: ethyl acetate (9:1) affording the product as a pale brown oil (46.0g, 92%).

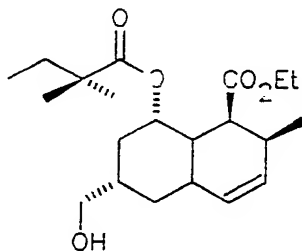
5 TLC: RF 0.33 (hexane: ethyl acetate, 4:1).

delta <sub>H</sub> 5.55 (1H, m), 5.47 (1H, d, J 10.3 Hz), 5.43 (1H, m), 4.11 (2H, q, J 7.2 Hz), 3.67 (3H, s), 2.73 - 2.46 (5H, m), 2.32 (1H, br d, J 13.5 Hz), 1.91 (1H, ddd, J 15.2, 7.2, 2.9 Hz), 1.7 - 1.61 (1H, m), 1.49 (2H, q, J 7.5 Hz), 1.24 (3H, t, J 7.2 Hz), 1.31 - 1.19 (1H, m), 1.09 (3H, s), 1.07 (3H, s), 0.89 (3H, d, J 6.7 Hz), 0.81 (3H, t, J 7.5 Hz)

15 Step 3

Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-6-hydroxymethyl-2-methyl-8-(2,2-dimethylbutyryloxy) naphthalene-1-carboxylate.

20



30 Lithium triethylborohydride (1 M solution in THF; 337 mmol; 2.1 equivalents) was added over approx 20 minutes to a stirred solution of the triester from step 2 (63.2g, 160.5 mmol) in dry THF (800 mL) under argon, at between 5°C and 0°C. After 1 hour, saturated ammonium chloride solution (250 mL) was added and the mixture allowed to

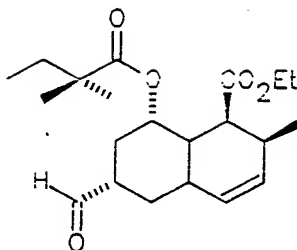
warm to room temperature, with stirring. The THF was evaporated under reduced pressure and the residue extracted with ethyl acetate (3 x 300 mL). The combined ethyl acetate extracts were washed vigorously with 2M  
5 hydrochloric acid (250 mL), followed by saturated sodium bicarbonate solution (250 mL) and brine (100 mL) and dried. Evaporation under reduced pressure gave a gum, which was dissolved in methanol (250 mL). The solution  
10 was heated to approx 50°C, then the methanol evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with ethyl acetate:hexane (1:4 to 1:2) to give the product (10) as a white solid ((56.7g, 96%).

15 Tlc: RF 0.21 (30% ethyl acetate/hexane)

delta <sub>H</sub> 5.64 - 5.58 (1H, m), 5.44 - 5.40 (2H, m), 4.18 -  
4.05 (2H, m), 3.82 (1H, t, J 10.0 Hz), 3.59 (1H, dd, J  
10.5, 5.8 Hz), 2.67 - 2.55 (2H, m), 2.45 - 2.26 (1H, m),  
20 2.10 - 1.18 (12H, complex m), 1.15 (3H, s), 1.14 (3H, s),  
0.91 (3H, d, J 6.9 Hz), 0.84 (3H, t, J 7.5 Hz)

#### Step 4

25 Ethyl(1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-  
6-formyl-2-methyl-8-(2,2-dimethylbutyryloxy) naphthalene-  
1-carboxylate.



5

10 A solution of the alcohol from step 3 (56.7g, 154.8 mmol) in dry dichloromethane (2 x 400 mL) was added via cannula to a stirred mixture of finely ground pyridinium dichromate (86.8g, 230.8 mmol) and freshly activated finely ground 3A molecular sieves (28.4g) under argon.

15 The mixture was cooled in a cold-water bath and dry acetic acid (15.5 mL) added slowly. After 80 minutes, diethyl ether (3 L) was added and the mixture filtered through Kieselguhr (to remove most of the insoluble chromium salts) before passing the filtrate down a

20 Florisil (60 - 100 mesh) column. (The word FLORISIL is a trade mark). The column was eluted with excess diethyl ether, which was evaporated and the residue azeotroped with toluene to leave the aldehyde as a pale yellow oil, which crystallised (55.5g, 98.4%)

25

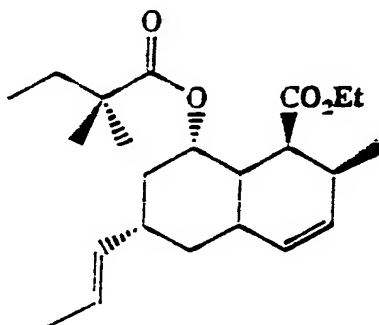
Tlc: RF 0.37 (SiO<sub>2</sub> 30% ethyl acetate/hexane).

30

delta <sub>H</sub> 9.65 (1H, d, J 1 Hz), 5.62 - 5.44 (3H, m), 4.12 (2H, q, J 7.1 Hz), 2.59 - 2.24 (7H, m), 2.08 - 1.99 (1H, m), 1.66 (1H, td, J 10.9, 1.6 Hz), 1.49 (2H, qd, J 7.7, 2.3 Hz), 1.23 (3H, t, J 7.4 Hz), 1.09 (3H, s), 1.07 (3H, s), 0.89 (3H, d, J 6.8 Hz), 0.80 (3H, t, J 7.4 Hz)

Step 5

Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-8-(2,2-dimethylbutyryloxy)-6-[(E)-prop-1-enyl] naphthalene-1-carboxylate.



THF (1000 mL) was added to chromium (II) chloride (112.2g, 0.91 mol) under an argon atmosphere. After stirring the mixture until a fine suspension resulted, a solution of the aldehyde from step 4 (41.6g, 0.11 mol) and 1,1-diiodoethane (64.4g, 0.23 mol) in THF (500 mL) was added. The reaction mixture was stirred for 15 hours, then water (750 mL) was added and stirring continued for 5 minutes. The THF was removed under reduced pressure and the aqueous mixture extracted with ether 3 x 500 mL). The combined ethereal layers were washed with brine (500 mL) and dried and evaporated under reduced pressure, leaving a green oil. This was purified by chromatography on silica eluting with hexane: ethyl acetate, (19:1 to 9:1), giving the product as a colourless oil (35.1g, 82%).

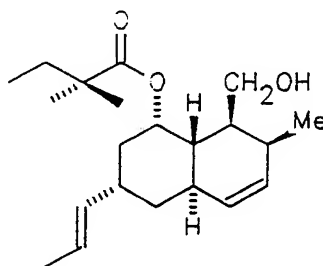
Tlc: RF 0.34 (hexane: ethyl acetate, 9:1)

$\delta_H$  5.83 - 5.73 (1H, m), 5.63 - 5.57 (1H, m), 5.46 -

5.32 (3H, m), 4.18 - 4.06 (2H, m), 2.68 (1H, dd, J 11.4, 5.9 Hz), 2.70 - 2.43 (3H, m), 2.0 - 1.37 (7H, complex m), 1.63 (3H, dt, J 6.5, 1.1 Hz), 1.24 (3H, t, 7.0 Hz), 1.15 (3H, s), 1.14 (3H, s), 0.91 (3H, d, J 6.9 Hz), 0.83 (3H, t, J 7.4 Hz)

### Step 6

(1S,3S,4aR,7S,8S,8aS)-1,2,3,4,4a,7,8,8a-octahydro- 8-hydroxymethyl-7-methyl-3-[(E)-prop-1-enyl]-1-naphthalenyl 2, 2-dimethylbutyrate.



20

A solution of the ester from step 5 (35.1g) 93.3 mmol) was stirred in THF (350 mL) at -78°C while a solution of lithium triethylborohydride in THF (1 M, 280 mL, 280 mmol) was added. The reaction mixture was allowed to warm to 4°C and left for 14 hours. Saturated aqueous ammonium chloride solution (500 mL) was cautiously added, the THF removed under reduced pressure and the resulting aqueous mixture extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with 2M aqueous hydrochloric acid solution (500 mL) and brine (250 mL), and then dried and evaporated under reduced pressure. The residue was dissolved in methanol (100 mL) and the solution heated at 50°C for 10 minutes and then

evaporated. This procedure was repeated once the residual pale yellow oil (29.6g) was purified by chromatography on silica eluting with hexane: ethyl acetate, (gradient from 85:15: to 0:100, affording the product as a white solid (18.1g, 58%), followed by the over-reduction product.

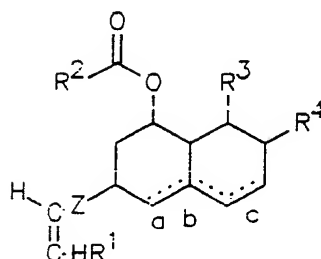
Tlc: RF 0.54 (hexane:ethyl acetate, 1:1).

10      $\delta_{\text{H}}$  5.77 (1H, ddq, J 15.2, 8.2, 1.6 Hz), 5.65 (1H, ddd, 9.8, 4.8, 2.6), 5.45 - 5.31 (2H, m), 5.04 (1H, m), 3.64 (1H, dd, J 10.4, 4.85 Hz), 3.49 (1H, t, J 9.8 Hz), 2.58 2.50 (3H, m), 2.01 - 1.89 (2H, m), 1.8 - 1.22 (10H, complex m), 1.17 (3H, s), 1.16 (3H, s), 0.94 (3H, d, J 6.9 Hz), 0.86 (3H, t, J 7.1 Hz)

20     It can therefore be seen that the invention provides a simple and convenient route for the production of compounds of general formula IV which are useful intermediates in the production of mevinic acids.

CLAIMS

1. A process for the preparation of a compound of general formula I



I

wherein  $R^1$  represents a  $C_{1-8}$  alkyl group;

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{1-8}$  hydroxyalkyl,  $C_{1-8}$  alkylthio, phenyl, substituted phenyl group or  $C_{1-6}$  alkyl substituted with an optionally substituted phenyl group.

$R^3$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl,  $CO_2(C_{1-8})$ alkyl,  $CO_2(C_{2-8})$ alkenyl,  $C_{1-8}$  alkylthio,  $(C_{1-2})$ alkyl  $CO_2(C_{1-8})$ alkyl or  $C_{1-8}$  aldehydoalkyl where the aldehyde function is protected by a suitable protecting group (for example, an acetal such as a dimethyl acetal);

$R^4$  represents a hydrogen atom,  $C_{1-8}$  alkyl or  $C_{2-8}$  alkenyl;

Z represents a group  $(CH_2)_n$  or a branched alkyl chain;  
n is 0 to 8

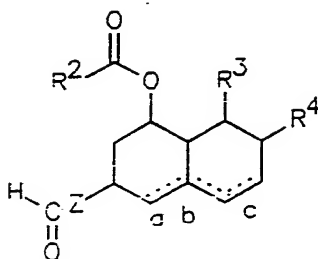
and each of a, b and c is independently a single or a

double bond;

the process comprising reacting a compound of general formula II

5

10



II

15 wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula I; with a compound of general formula III



20 wherein  $R^1$  is as defined in general formula I;

in the presence of metal ions such as chromium (II) ions.

2. A process as claimed in claim 1 wherein the source  
25 of chromium (II) ions is chromium (II) chloride.

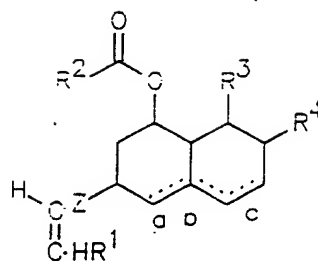
3. A process as claimed in claim 1 or claim 2 wherein the reaction is carried out in tetrahydrofuran.

30 4. A process as claimed in any preceding claim wherein  $R^1$  is a methyl group.

5. A compound of general formula I



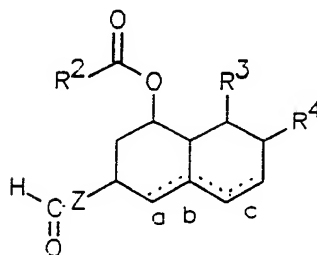
31



I

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $n$ ,  $a$ ,  $b$  and  $c$  are as defined in claim 1.

6. A compound of general formula II.



II

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $n$ ,  $a$ ,  $b$  and  $c$  are as defined in claim 1.

7. A compound as claimed in claim 5 or claim 6 wherein, independently or in any compatible combination,

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl or  $C_{1-8}$  hydroxyalkyl;

$R^3$  represents  $\text{CO}_2\text{C}_{1-8}$  alkyl;

$R^4$  represents a methyl group;

5      $Z$  is  $(\text{CH}_2)_n$ ;

$n$  is 0;

10      $a$  and  $b$  are single bond and  $c$  is a double bond; and  
in compounds of formula I,  $R^1$  is a methyl group.

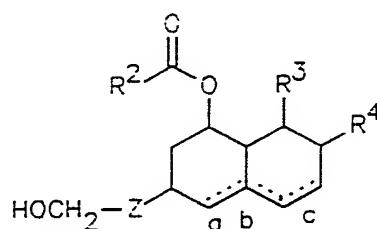
15     8. Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8, 8a-octahydro-6-[(E)-prop-1-enyl]-2-methyl-8-(2, 2-dimethylbutyryloxy) naphthalene-1-carboxylate; or

ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8, 8a-octahydro-6-formyl-2-methyl-8-(2, 2-dimethylbutyryloxy) naphthalene-1-carboxylate.

20

9. A process for the synthesis of a compound of general formula V

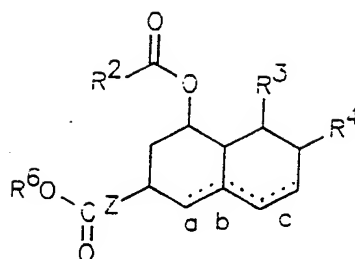
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V

30

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula I the process comprising reacting, with a reducing agent a compound of general formula VI



VI

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$ ,  $c$  are as defined in general formula I and  $R^6$  is  $C_{1-8}$  alkyl and wherein, in general formula VI at least the ester group at the 8- position is unprotected.

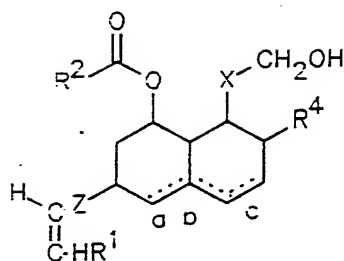
10. A process as claimed in claim 9 wherein  $R^3$  is a  $CO_2(C_{1-8})$ alkyl group.

11. A process as claimed in claim 9 or claim 10 wherein the reducing agent comprises lithium aluminium hydride or an alkyl derivative thereof or lithium borohydride or an alkyl derivative thereof.

12. A process as claimed in claim 11 wherein the reducing agent is lithium triethylborohydride.

13. A process for the preparation of a compound of formula IV

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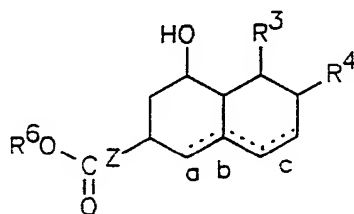


IV

wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula I;

$X$  is  $(CH_2)_m$  or a branched alkyl chain and  $m$  is 0 to 2, the process comprising the steps of:

A. converting a compound of general formula VII



VII

wherein  $R^3$ ,  $R^4$ ,  $Z$ ,  $a$ ,  $b$  and  $c$  are as defined in general formula I and  $R^6$  is  $C_{1-8}$  alkyl;

to a compound of general formula VI as defined above by acylation with a suitable acylating agent;

B. converting a compound of general formula VI to a

compound of general formula V by a process as claimed in any one of claims 9-11.

5 C. conversion of a compound of general formula VI to a compound of general formula II by oxidation with a mild oxidising agent;

10 D. conversion of a compound of general formula II to a compound of general formula I by a process as claimed in any one of claims 1 to 3;

15 E. conversion of a compound of general formula I wherein  $R^3$  is an ester group to a compound of general formula IV by reduction with a suitable reducing agent.

20 14. A process as claimed in claim 13, wherein the reducing agent used in step E is lithium aluminium hydride or an alkyl derivative thereof or lithium borohydride or an alkyl derivative thereof.

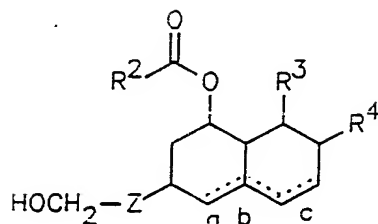
15 15. A process as claimed in claim 14 wherein the reducing agent is lithium triethylborohydride.

25 16. A process as claimed in any one of claims 13 to 15 wherein, in step C, the oxidising agent is pyridinium dichromate.

30 17. A process as claimed in claim 16 wherein the oxidation of step C is carried out in the presence of activated molecular sieves and acetic acid.

18. A process as claimed in claim 16 or claim 17 wherein the solvent for step C is dichloromethane.

19. A compound of general formula V



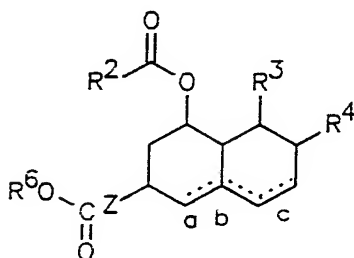
V

10

wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , Z, a, b and c are as defined in claim 1.

15

20. A compound of general formula VI



VI

25

wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , Z, a, b and c are as defined in claim 1.

30

21. A compound of general formula IV as defined in claim 13 wherein m is 1 or 2.

22. A compound as claimed in claim 19 or claim 20

wherein:

$R^2$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl or  $C_{1-8}$  hydroxyalkyl;

5

$R^3$  represents  $CO_2(C_{1-8})$  alkyl;

$R^4$  represents a methyl group;

10

Z is  $(CH_2)_n$ ;

n is 0; and

15

a and b are single bonds and c is a double bond; and

in compounds of formula VI,  $R^6$  is methyl.

20

23. Ethyl (1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8, 8a-octahydro-6-[(E)-prop-1-enyl]-2-methyl-8-(2, 2-dimethylbutyryloxy) naphthalene-1-carboxylate; or

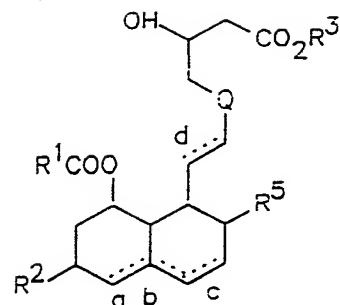
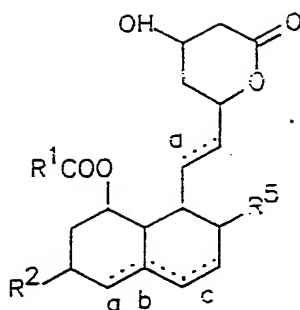
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ethyl(1S,2S,4aR,6S,8S,8aS)-1,2,4a,5,6,7,8,8a-octahydro-6-formyl-2-methyl-8-(2,2-dimethylbutyryloxy)naphthalene-1-carboxylate.

30

24. A process for the preparation of a compound of formula IX or X

5



10      wherein

$R^1$  represents a  $C_{1-8}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl( $C_{1-8}$ )alkyl,  $C_{2-8}$  alkenyl, or  $C_{1-6}$  alkyl substituted phenyl group;

15

$R^2$  represents a  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl, group or a  $C_{1-5}$  alkyl,  $C_{2-5}$  alkenyl, or  $C_{2-5}$  alkynyl group substituted with a substituted phenyl group;

20

$R^3$  represents a hydrogen atom or a substituent  $R^4$  or M;

$R^4$  represents a  $C_{1-5}$  alkyl group, or a  $C_{1-5}$  alkyl group substituted with a group chosen from substituted phenyl, dimethylamino and acetylamino;

25

$R^5$  represents a hydrogen atom or a methyl or ethyl group, except that when  $R^2$  is methyl then  $R^5$  is not methyl;

30

M represents a cation capable of forming a pharmaceutically acceptable salt;

Q represents C=O or CHOH; and

each of a, b, c, and d is independently a single or



double bond except that when a and c are double bonds then b is a single bond;

5 the process comprising converting a compound of formula IV to a compound of formula VII by a process as claimed in any one of claims 13 to 18, followed by converting a compound of VII to compounds of formulae IX and X by any suitable method.


10 25. A process as claimed in claim 23 for the preparation of

15 (1S, 2S, 4aR, 6S, 8S, 8aS, 4'R, 6'R)-6'-{2- (1,2,4a, 5,6,7,8,8a-octahydro-2-methyl-8- [2''-dimethyl- 1''-oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)ethyl}-tetrahydro-4'-hydroxy-2H-pyran-2'-one.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 92/00920

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5	C07C69/757; C07C69/013;	C07C69/732; C07C67/29;
		C07C67/343; C07D309/30
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	WO,A,9 100 280 (BRITISH BIOTECHNOLOGY LIMITED) 10 January 1991 cited in the application see page 26, line 5 - page 28, line 29 see figure 4	1
A	EP,A,0 251 625 (MERCK AND CO. INC.) 7 January 1988 cited in the application see claims	1
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
04 AUGUST 1992	19. 08. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	KINZINGER J.M. 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9200920  
SA 59565

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 04/08/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9100280	10-01-91	AU-A- 6032290	17-01-91
		EP-A- 0480986	22-04-92
EP-A-0251625	07-01-88	AU-A- 7455987	24-12-87
		JP-A- 63072652	02-04-88
		US-A- 4940727	10-07-90
		ZA-A- 8704487	23-12-87